Exhibit F

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Vitamin-D3 derivatives and breast-tumor cell growth: effect on intracellular calcium and apoptosis.

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Vitamin-D3 derivatives are now well-recognized growth inhibitors of numerous tumoral cells and in particular breast-cancer cells. However, the mechanisms by which they operate are not well established. Among the wide range of physiological and biological functions of vitamin-D3 derivatives, the best described include their action on calcium homeostasis. In this study, we sought to establish whether the effects of vitamin-D3 derivatives on breast-cancer cell growth may be in part related to intracellular calcium modulation and induction of apoptosis. To address these questions, we used, in addition to 1,25(OH)2D3, the active metabolite of vitamin D3, a non-calcemic 1,25(OH)2D3 derivative: Ro 23-7553 [16-ene-23-yne-1,25(OH)2D3], which in our hands was more potent than the parent compound in inhibiting breast-cancer cell growth. We showed that the efficiency of both compounds in growth inhibition was higher in the estradiol-receptor-positive-breast-tumor MCF-7 cells than in the estradiol-receptor-negative MDA-MB 231 cells. In MCF-7 cells in particular, important modifications of intracellular calcium related to the emptying of intracellular pools were observed. The depletion of Ca++ from intracellular stores was followed by the induction of apoptosis. Such a phenomenon was never observed in MDA-MB 231 cells. Our results suggest that the action of vitamin-D3 derivatives on the depletion of calcium stores, which was more significant in MCF-7 than in MDA-MB 231 cells, may induce apoptosis in the former cells and account for the high efficiency of vitamin-D3 derivatives on growth inhibition of MCF-7 breast-tumor cells.